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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/720,039 | 11/20/2003 | Richard M. Kream | | 2539 |

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| EXAMINER | |
|---|---|
| LANDSMAN, ROBERT S | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 12/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/720,039 | KREAM, RICHARD M. | |
| | Examiner | Art Unit | |
| | Robert Landsman | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *20 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 11/20/03 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/20/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *1. Formal Matters*

A. The Preliminary Amendment, filed 12/20/04, has been entered into the record.

B. Claims 1-4 are pending and are the subject of this Office Action.

### *2. Information Disclosure Statement*

A. Reference to U.S. Application Serial No. 09/428,692, submitted on the IDS filed 11/20/03, has been lined through since this application is not a U.S. Patent, nor is it in the inventor's name, nor commonly assigned. Furthermore, this application has issued as a U.S. Patent. Therefore, the Examiner has cited this document on a Form 892.

B. Foreign Patent Document, 11060598, on the IDS filed 11/20/03, has been lined through since no country of filing has been identified.

### *2. Specification*

A. The specification is objected to since Update the first line of the spec re:10/134,187

B. The specification is objected to. It is suggested that the Brief Description of Figures 1 and 2 be in separate paragraphs.

### *3. Claim Objections*

A. In line 2 of claim 1, after the term "subject" the word "of" should be deleted.

B. In claim 1, it is suggested that part (a) read "selecting" instead of "the selection of." Since this is a method claim, the active form of the verb would be more appropriate. A similar form should be followed for parts (b) and (c).

C. In claim 1a, it is believed that the term "mu (m) opioid receptor is modified" should read "mu (m) opioid receptor agonist is modified."

***4. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing morphine conjugated to a full-length substance P peptide, does not reasonably provide enablement for a method of producing any non-peptide opioid conjugated to any active substance P fragment, or any peptide in general, for transport across the BBB. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The breadth of the claims is excessive. The Examiner was unable to find an "Examples" section in the specification. Starting on page 23 of the specification, it appears that Applicants have produced various opioid-SP fragments with various hinges, e.g.

> Morphine is chemically modified by covalent attachment at its 6'OH group to the hinge-forming organic molecules described above: d-glucuronic acid, succinic acid, gamma-hydroxy butyric acid.

The specification discussed chemically modified morphine derivatives and pharmacologically active SP fragments as well as numerous linkers (hinges). However, it is not clear if these were actually made, nor is it clear if these conjugates are able to cross the BBB. Respectfully, it appears that Applicants have only provided suggestion on how to link morphine to SP using a limited number of linkers (see also Table 1 on page 20). Applicants have provided no guidance or working examples of **(1) other non-peptide opioids (2) linked to anything other than a full-length SP peptide (3) using any linker other than that in Table 1.** Applicants have not shown which regions of SP are required in order to maintain the pharmacological activity of full-length SP, nor have they shown that non-peptide opioids other than morphine can be linked to SP via the large scope of linker claimed. Furthermore, Applicants have not

demonstrated that these conjugates, including which of the large breadth of non-peptide opioids as well as hinge linkers, are able to **cross the BBB.** Furthermore, Applicants have not taught what types of **"modifications"** (see claim 1) can be made to the non-peptide opioid in order for it to be covalently attached to cross-linker.

***5. Claim Rejections - 35 USC § 112, first paragraph – written description***

A. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims. The claims recite a method of transporting a peptide across the BBB by linking it to a non-peptide opioid via a flexible hinge linker. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Thus the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification only discloses the concept of using morphine linked to a full-length SP peptide via d-glucuronic acid, succinic acid, gamma-hydroxy butyric acid. It is noted, however, that this concept is not adequately described other than, respectfully, by a mere suggestion.

Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus, including the types of linkers used, or for the range of opioid compounds recited in claim 2. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, "a non-peptide opioid conjugated to a peptide via a flexible hinge linker" is insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

***6. Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

A. Claims 1-4 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 6,881,829. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the application and patent claim non-peptide opioids such as morphine conjugated via a flexible hinge linker to a peptide, such as SP. The patent claims pharmaceutical compositions, which, in view of the properties of non-peptide opioids and SP, would inherently cross the BBB.

B. Claims 1-4 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 6,759,520. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the application and patent claim non-peptide opioids such as morphine conjugated via a flexible hinge linker to a peptide, such as SP. The patent claims pharmaceutical compositions, which, in view of the properties of non-peptide opioids and SP, would inherently cross the BBB.

*7. Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

A. Claims 1-4 are rejected under 35 U.S.C. 102(e) as being anticipated by Carr et al. (U.S. Patent 6,759,520). The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

B. Claims 1-4 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. The present invention and U.S. Patent 6,759,520 have one common inventor, Richard Kream. However, the patent and the application are not commonly owned.

*8. Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wainer et al. (Science 176:1143-1145, 1972) in view of Foran et al. (PNAS 13:7621-7626, 2000). The claims recite a method of

transporting a peptide across the BBB by conjugating it to a non-opioid peptide and a flexible hinge linker.

Wainer teach a conjugate in which morphine (a non-peptide opioid) is linked to a peptide (BSA via a succinyl bond (Abstract). Wainer do not teach the conjugation of morphine to SP. However, Foran teach an opioid/SP receptor chimera in which the opioid is a peptide, not an alkaloid. It would have been obvious to one of ordinary skill in the art at the time of the present invention to have substituted the BSA of Wainer for the SP of Foran for use in permitting SP to cross the BBB since both SP and non-peptide opioids such as morphine are known to act centrally; therefore, requiring transport across the BBB. Since both BSA and SP are peptides, the artisan would have been motivated to replace one peptide with another for the purpose desired by the artisan since the procedure for linking peptides to linkers such as succinic acid were already known at the time of the present invention, as evidenced by Wainer. Furthermore, it would have been obvious to provide a linker such that the opioid and substance P moieties would be able to bind to their respective receptors at the same time in order to obtain the maximum benefit of both compounds. Similarly, the conjugation of opioids to SP peptides was well-known at the time of the present invention, as seen by Foran. Therefore, replacing the peptide opioid of Foran with the non-peptide opioid of Wainer would have been obvious since, these compounds are both opioids and have the same analgesic properties and non-peptide opioids have the inherent property of crossing the BBB due to their lipophilicity.

***9. Conclusion***

A. No claim is allowable.

***Advisory information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (571) 272-0888. The examiner can normally be reached on T-F 10 AM – 7 PM (eastern).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert Landsman
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Art Unit 1647